Relative importance of genetic effects in rheumatoid arthritis: historical cohort study of Danish nationwide twin population

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Abstract

Objective To determine the relative importance of environmental and genetic effects in the development of rheumatoid arthritis.
Design Historical cohort study with record linkage between a twin registry and the Danish discharge registry as well as the Danish national registry of deaths used to estimate completeness.
Setting Two population based nationwide twin birth cohorts.
Participants 37 338 twins were sent a questionnaire about rheumatic diseases. Self reported rheumatoid arthritis was verified by clinical examination and from medical records.
Main outcome measures The probandwise concordance rate of rheumatoid arthritis in monozygotic and dizygotic twins.
Results The response rate was 84.7%. Rheumatoid arthritis was verified in 13 monozygotic and 36 dizygotic twins. There were no concordant monozygotic twin pairs and two concordant dizygotic twin pairs. Based on capture-recapture methods the probability of ascertainment was 78.3%. The probandwise concordance rate was 0 (95% confidence interval 0 to 24.7) in monozygotic twins and 8.8 (1.9 to 23.7) in dizygotic twins.
Conclusion Genes are of minor importance in the development of rheumatoid arthritis.

Introduction

Rheumatoid arthritis is a systemic inflammatory autoimmune disease of unknown cause. Environmental and genetic risk factors have been identified, but no single risk factor has emerged as necessary or sufficient to cause the disease.

Twin studies represent one of the simplest ways to unravel the relative importance of genetic and environmental effects. In studies of specific diseases or traits in twins who volunteer to take part, monozygotic, concordant, and female twins tend to be overrepresented.[1 2] Hence, much of the available literature on rheumatoid arthritis in twins overestimates the contribution of genetic factors.[3–5] Only two previous studies were population based, but confirmation of the diagnosis according to validated classification criteria was not performed.[1 6]

We undertook a nationwide study among twins in Denmark to estimate the importance of genetic effects in the development of rheumatoid arthritis.

Methods

Ascertainment of twins

The study comprised two nationwide twin populations. The older birth cohort comprised 1631 same sex pairs of twins born 1921-40 in which both twins were alive in 1994.[7] The younger birth cohort comprised 34 076 surviving twins from same and opposite sex pairs of twins born 1953-82.[7] To estimate a possible selection bias introduced by the requirement that both twins had to be alive we also sent questionnaires to 990 surviving individuals from same sex twin pairs born 1921-30.

Ascertainment and verification of rheumatoid arthritis

In 1994 the twins were asked by questionnaire if they had ever suffered from rheumatoid arthritis. Twins who reported that they had rheumatoid arthritis subsequently received a clinical profile questionnaire followed by a telephone interview. If rheumatoid arthritis could not be ruled out they were asked for permission to approach their non-affected cotwin. Both twins were invited to have a clinical examination. They underwent a structured interview and clinical examination, and blood samples were drawn for measurement of rheumatoid factor, HLA typing, and determination of zygosity.

All participants gave informed consent and permission for us to collect information from medical records. We used the modified 1987 revised criteria of the American Rheumatism Association to confirm the diagnosis.[8] Time of onset was defined as the time when the diagnosis was established for the first time according to either the patient or a physician. Time of discordance was defined as the time from onset in one twin until onset in the second twin or the end of observation.

Laboratory techniques

We established zygosity by blood group analysis. Monozygotic twins are same sex pairs with complete

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Table 1 Number of criteria for rheumatoid arthritis* present in cohort of twins

No of criteria†	No (%) of twins	Cumulative No (%) of twins
7	2 (2.8)	2 (2.8)
6	16 (22.2)	18 (25.0)
5	19 (26.4)	37 (51.4)
4	12 (16.7)	49 (68.1)
3	6 (8.3)	55 (76.4)
2	11 (15.3)	66 (91.7)
1	5 (6.9)	71 (98.6)
0	1 (1.4)	72 (100.0)

*American Rheumatism Association 1987 revised criteria.
†To be classfied as having rheumatoid arthritis patients had to fulfil four or more criteria.

blood group concordance; <0.5% of dizygotic pairs have this concordance.[9] Genomic DNA was prepared from peripheral blood lymphocytes and amplified by polymerase chain reaction. We used sequence specific primers for the detection of the currently recognisable HLA alleles associated with rheumatoid arthritis, which are characterised by one common epitope (the shared epitope).[10] We used enzyme linked immunosorbent assay (ELISA) with human IgG as antigen to detect the presence of rheumatoid factor.

Validation of completeness

We used record linkage with the Danish discharge registry to find any twins with rheumatoid arthritis that we had not already identified. The record linkage included twins discharged with a diagnosis of rheumatoid arthritis since 1977, and the diagnosis was subsequently validated by examination of discharge papers or telephone interview, or both. We estimated the completeness of the study with capture-recapture.[11]

We linked records of the twin registry and the Danish national registry of deaths to identify any twins with rheumatoid arthritis who had died between 1951 and 1995. We sent a questionnaire to individual twins who would have been eligible for participation except for the death of their cotwin. The surviving twin was asked whether he or she or the deceased cotwin had ever had rheumatoid arthritis.

Ethics

The study was approved by all the regional scientific ethics committees in Denmark and the Danish data protection board.

Analysis

There are three different measures of concordance used in twin studies. As there are always different degrees of ascertainment only the probandwise concordance rate should be used as it is robust against incomplete ascertainment compared with the pairwise and casewise concordance rates,[12 13] which always tend to inflate the importance of genetic factors. Thus, in our study a proband was a twin who independently of his or her cotwin reported rheumatoid arthritis and who fulfilled our classification criteria for rheumatoid arthritis. A secondary case was a twin ascertained through a cotwin and who fulfilled our classification criteria for rheumatoid arthritis. We excluded pairs of twins who both had rheumatoid arthritis and neither twin fulfilled the proband criteria.

We had four categories of twin pairs with at least one affected member. Concordant pairs were classified into one of four groups: pairs in which neither affected twin fulfilled the proband criteria (C0); singly ascertained concordant pairs—that is, one affected twin was a proband and the other a secondary case (C1); and doubly ascertained concordant pairs—that is, both affected twins were probands (C2). For discordant pairs the affected twin fulfilled the proband criteria (D1).

We calculated probandwise concordance rate as $(C1 + 2C2)/(C1 + 2C2 + D1)$ and pairwise concordance rate as $(C1 + C2)/(C1 + C2 + D1)$. All estimates are given with 95% confidence intervals.

Results

The overall response rate after one reminder was 75% (2445/3262) in older twins and 86% (29 433/34 076) in younger twins. The response rate for both twins from a pair was higher among monozygotic twin pairs (4210/5194, 81%) than among dizygotic same sex pairs (5129/6961, 74%) and dizygotic opposite sex pairs (3769/5513, 68%). Slightly more women than men responded (16 639/19 167 (87%) *v* 15 239/18 575 (82%)). One hundred and fifty twins said they had rheumatoid arthritis. At the telephone interview 62 had no signs of arthritis, eight did not respond, six could not be traced, four declined to participate in a clinical examination, and one had died. The 69 remaining twins, in addition to three twins recruited through secondary sources, and 60 cotwins, agreed to a clinical examination. The participating twins were examined by AJS at home, at work, or in hospital. One twin declined to donate a blood sample. From the 72 candidate cases, 49 satisfied the modified criteria of the American Rheumatism Association (table 1).

Table 2 gives details of the twins with rheumatoid arthritis. There were no significant differences between monozygotic and dizygotic twins regarding sex, age, age at onset, mean discordance time, presence of rheumatoid factor, bony erosions, or shared epitope. Nodules were present more often in monozygotic twins than in dizygotic twins.

In one dizygotic twin pair, the twin with self reported rheumatoid arthritis was not affected, whereas the cotwin, who had not reported having rheumatoid arthritis, did fulfil the classification criteria for rheumatoid arthritis. As this pair was not presented by a proband we excluded them from the analysis. Table 3 shows the probandwise and pairwise concordance rates. There was no difference between monozygotic and dizygotic twin pairs in the rates. The probandwise concordance rate was 0 (95% confidence

Table 2 Distribution of demographic and clinical data in cases of twins with rheumatoid arthritis according to zygosity. Figures are numbers (percentage) of individuals unless stated otherwise

Characteristic	Monozygotic (n=13)	Dizygotic (n=36)	95% CI for difference
Women	9 (69.2)	25 (69.4)	–29.5% to 29.0%
Mean (SD) age (years):			
Older cohort (born 1921-40)	68.0 (2.7)	67.2 (3.3)	–1.9 to 3.5
Younger cohort (born 1953-82)	31.2 (5.8)	35.1 (5.1)	–10.0 to 2.2
Mean (SD) age at onset (years)	40.5 (20.7)	44.1 (15.1)	–14.4 to 7.4
Mean (SD) discordance time (years)	13.3 (13.4)	13.7 (10.87)	–8.0 to 7.3
Ever positive for rheumatoid factor	12 (92.3)	29 (80.6)	–7.7% to 31.2%
Ever had erosions	9 (69.2)	24 (66.7)	–26.9% to 32.0%
Ever had nodules	10 (76.9)	15 (41.7)	7.3% to 63.3%
Positive for shared epitope*	9 (69.2)	26 (74.3)	–34.0% to 23.9%

*Known for 35 dizygotic twins as one dizygotic twin pair refused to give blood samples.

Table 3 Probandwise and pairwise concordance rates* (95% confidence interval) of rheumatoid arthritis in twins according to zygosity

Zygosity	Probandwise	Pairwise
Monozygotic	0 (0 to 24.7)	0 (0 to 24.7)
Dizygotic	8.8 (1.9 to 23.7)	5.9 (0.7 to 19.7)

*No difference in probandwise concordance rate between monozygotic and dizygotic twins (95% CI −0.7 to 18.4).

interval 0 to 24.7) in monozygotic twins and 8.8 (1.9 to 23.7) in dizygotic twins.

The record linkage study identified 46 twins with possible rheumatoid arthritis, but in 23 cases the diagnosis could not be verified. Among the remaining 23 twins, we had already identified 18 and identified five solely through the Danish discharge registry. On the basis of the capture-recapture model our questionnaire had an estimated probability of ascertainment of 78.3%, and hence nine cases (95% confidence interval 3 to 16) may have been missed. We found no concordant monozygotic pairs through the Danish discharge registry.

The response rate from twins whose cotwin had died was 73.5%. There was no difference in response rate between monozygotic and dizygotic twins nor between men and women. Table 4 shows pairwise concordance because twin pairs in which one twin had died cannot fulfil the proband criteria. There was no difference in concordance for rheumatoid arthritis between monozygotic and dizygotic twin pairs.

From the record linkage study with the registry of deaths we identified six twins from six different twin pairs. In three cases the cotwins of the dead twins who had had rheumatoid arthritis were still alive and responded to the questionnaire. In one case a dizygotic twin pair was concordant for rheumatoid arthritis according to self report. We found no monozygotic concordant pairs.

Discussion

In this large twin study monozygotic twins were no more likely to be concordant for rheumatoid arthritis that dizygotic twins. Our results do not support a genetic contribution to the development of rheumatoid arthritis.

This is the first study to combine the recruitment of twins with rheumatoid arthritis through a questionnaire sent to a population based random sample with a subsequent clinically based validation of the diagnosis. We may not have found some concordant twin pairs with rheumatoid arthritis. Among pairs of twins in which one twin had died we found four pairs of monozygotic twins and three pairs of dizygotic twins who were concordant for self reported disease. The positive predictive value of self reported rheumatoid arthritis, however, is less than one third[14 15]—that is, of people who claim to have rheumatoid arthritis only one in three will actually have it—and the report of disease on behalf of family members is probably less accurate. It is therefore unlikely that the exclusion of pairs in which one twin had died had any impact on our results. The record linkage between the twin registry and both the national discharge registry and the national register of deaths identified no concordant monozygotic twin pairs and only one possible concordant dizygotic twin pair. Using these alternative and independent recruitment sources we found no monozygotic concordant pairs among non-responders or dead twins.

Cross sectional studies cannot show the lifetime risk for cotwins, but this does not imply any bias as long as the mean and distribution of discordance time does not differ between monozygotic and dizygotic twins, as in our study. None of the previously published twin studies on rheumatoid arthritis have dealt with this potential bias. The association between rheumatoid arthritis and HLA markers is related to age at onset and sex.[16 17] We did not find any difference in age at onset and sex between monozygotic and dizygotic probands, though rheumatic nodules, an indicator of more severe disease, were more common in monozygotic twins. The UK rheumatoid arthritis twin study is the only other such study that can reject this potential bias.[5] Even though our study was population based, twins with rheumatoid arthritis did not differ from twins recruited from clinical settings with regard to the traditional measures of severity, including HLA associated antigens.

The lack of concordant pairs could be due to observer bias, but this is unlikely as the cotwins in pairs discordant for disease did not show any signs of arthritis, and in most cases disease classification was based on medical records and blood samples, both of which are resistant to observer bias. We identified only a small number of twins with rheumatoid arthritis because participants were mostly young, with 90% of the twins born in 1952-83.

Our study had an estimated probability of ascertainment of 78%. As there is always bias in ascertainment towards monozygotic twin pairs and twin pairs concordant for specific diseases and traits, complete ascertainment would not change our estimate of concordance for rheumatoid arthritis.

Comparison with other studies

The Australian twin study was based on self reported rheumatoid arthritis without a clinical examination, and the sample of twins with rheumatoid arthritis had a high monozygotic:dizygotic ratio of 1.56 with an expected ratio of 0.5.[4] Only the pairwise concordance rates were presented.

The latest study of rheumatoid arthritis in twins in the United Kingdom included only volunteers.[5] In the United Kingdom for every pregnancy resulting in a live birth about one in 90 is of twins so on average about two in 90 people will be twins.[18] The prevalence of rheumatoid arthritis is 1%, so an estimated 19 monozygotic and 39 dizygotic pairs in would be concordant for rheumatoid arthritis simply by chance. The UK study identified 14 monozygotic and four dizygotic twin pairs concordant for rheumatoid arthritis, suggesting ascertainment bias towards monozygotic concordant pairs.

Table 4 Rate of concordance for self reported rheumatoid arthritis in twin pairs in which one twin had died

Zygosity	Concordant	Discordant	Pairwise concordance rate (95% CI)*
Monozygotic	4	10	28.6% (8.4% to 58.1%)
Dizygotic	3	27	10.0% (2.1% to 26.5%)
Unknown	1	10	—
Total	8	47	—

*Difference in rate between monozygotic and dizygotic pairs was 28.9% (3.7% to 61.5%).

What is already known on this topic

Rheumatoid arthritis is a multifactorial disease determined by both genetic and environmental factors

Previous twin studies have shown a higher concordance for rheumatoid arthritis in monozygotic than in dizygotic twins, but the results have been biased in favour of genetic effects

What this paper adds

As concordance for rheumatoid arthritis in this study was no more common in monozygotic twins than in dizygotic twins environmental effects may be more important than genetic effects in the development of rheumatoid arthritis

Two previous rheumatoid arthritis twin studies used a population based approach. In the Danish study from 1965 classification of rheumatoid arthritis was based on self report only.[1] In the Finnish twin study the diagnosis was based on the attending physician and not verified.[6] Thus, patients with, for example, ankylosing spondylitis might have been included, and in addition cotwins might have been diagnosed with rheumatoid arthritis on a less stringent basis if the index twin had already been diagnosed.

We acknowledge that our sample was relatively small, but we consider our results to be the most unbiased estimate of the genetic contribution to rheumatoid arthritis and support the observation of a weak familial aggregation.[19 20] Genetic makeup seems of minor importance in the development of rheumatoid arthritis.

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1 Harvald B, Hauge M. Hereditary factors elucidated by twin studies. In: Neel JV, Shaw MV, Schull WJ, eds. *Genetics and the epidemiology of chronic diseases.* Washington, DC: Department of Health, Education and Welfare, 1965:61-76 (Public Health Service Publication No 1163).
2 Lykken DT, Tellegen A, DeRubeis R. Volunteer bias in twin research: the rule of two-thirds. *Soc Biol* 1978;25:1-9.
3 Lawrence JS. Heberden oration, 1969. Rheumatoid arthritis—nature or nurture? *Ann Rheum Dis* 1970;29:357-79.
4 Bellamy N, Duffy D, Martin N, Mathews J. Rheumatoid arthritis in twins: a study of aetiopathogenesis based on the Australian twin registry. *Ann Rheum Dis* 1992;51:588-93.
5 Silman AJ, MacGregor AJ, Thomson W, Holligan S, Carthy D, Farhan A, et al. Twin concordance rates for rheumatoid arthritis: results from a nationwide study. *Br J Rheumatol* 1993;32:903-7.
6 Aho K, Koskenvuo M, Tuominen J, Kaprio J. Occurrence of rheumatoid arthritis in a nationwide series of twins. *J Rheumatol* 1986;13:899-902.
7 Kyvik KO, Christensen K, Skytthe A, Harvald B, Holm NV. The Danish twin register. *Dan Med Bull* 1996;43:467-70.
8 MacGregor AJ, Bamber S, Silman AJ. A comparison of the performance of different methods of disease classification for rheumatoid arthritis. Results of an analysis from a nationwide twin study. *J Rheumatol* 1994;21:1420-6.
9 Husby H, Holm NV, Gernow A, Thomsen SG, Kock K, Gurtler H. Zygosity, placental membranes and Weinberg's rule in a Danish consecutive twin series. *Acta Genet Med Gemellol (Roma)* 1991;40:147-52.
10 Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* 1987;30:1205-13.
11 Hook EB, Regal RR. Capture-recapture methods in epidemiology: methods and limitations. *Epidemiol Rev* 1995;17:243-64.
12 Holm NV. A note on ascertainment probability in the Allen/Hrubec twin model. *Acta Genet Med Gemellol (Roma)* 1983;32:37-47.
13 Smith C. Concordance in twins: methods and interpretation. *Am J Hum Genet* 1974;26:454-66.
14 Star VL, Scott JC, Sherwin R, Lane N, Nevitt MC, Hochberg MC. Validity of self-reported rheumatoid arthritis in elderly women. *J Rheumatol* 1996;23:1862-5.
15 Kvien TK, Glennas A, Knudsrod OG, Smedstad LM. The validity of self-reported diagnosis of rheumatoid arthritis: results from a population survey followed by clinical examinations. *J Rheumatol* 1996;23:1866-71.
16 Jaraquemada D, Ollier W, Awad J, Young A, Silman A, Roitt IM, et al. HLA and rheumatoid arthritis: a combined analysis of 440 British patients. *Ann Rheum Dis* 1986;45:627-36.
17 MacGregor A, Ollier W, Thomson W, Jawaheer D, Silman A. HLA-DRB1*0401/0404 genotype and rheumatoid arthritis: increased association in men, young age at onset, and disease severity. *J Rheumatol* 1995;22:1032-6.
18 Bryan EM. The role of twins in epidemiological studies. *Paediatr Perinat Epidemiol* 1992;6:460-4.
19 Del Junco D, Luthra HS, Annegers JF, Worthington JW, Kurland LT. The familial aggregation of rheumatoid arthritis and its relationship to the HLA-DR4 association. *Am J Epidemiol* 1984;119:813-29.
20 Barrera P, Radstake TR, Albers JM, van Riel PL, van De Putte LB. Familial aggregation of rheumatoid arthritis in the Netherlands: a cross-sectional hospital-based survey. European consortium on rheumatoid arthritis families (ECRAF). *Rheumatology (Oxford)* 1999;38:415-22.

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Commentary: Do genes or environment influence development of rheumatoid arthritis?

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The aetiology of rheumatoid arthritis, like several other chronic disorders, is widely accepted to be "multifactorial." This term suggests that the disease results from one or more environmental influences acting on a genetically susceptible background. Although the relative contributions of genetic and environmental influences are the source of several investigations, in the strictest sense, as with most other diseases, neither is enough on its own to explain onset of the disease.

The size of a genetic effect is typically estimated from the familal risk of recurrence, defined as the increased risk in first degree relatives of affected individuals compared with the background occurrence in the population. With this approach the genetic con-

tribution to rheumatoid arthritis is indeed small. The risk of recurrence in a sibling is possibly not much greater than 2,[1] substantially lower than that seen, for example, with other autoimmune disorders such as multiple sclerosis and thyroid disease.[2] An extension to that approach is to consider the comparative risk between identical and non-identical cotwins of affected individuals. The underlying hypothesis is that identical (monozygotic) and (same sex) non-identical (dizygotic) twins are similar in their sharing of the environment and hence the magnitude of any excess risk of disease in the monozygotic twins quantifies the genetic effect.

Two nationwide twin studies, one from Finland,[3] the other from the United Kingdom,[4] yielded similar concordance rates in monozygotic twins of around 15% four times greater than that seen in dizygotic twins. Indeed, from these two studies it was estimated that shared genetic factors in the monozygotic twins explained about 60% of the incidence of rheumatoid arthritis.[5] The assumption about similarity in environment between the two types of twins might not be true,[6] and hence this proportion represents the upper limit.

Against this background the results of Svendsen et al seem somewhat surprising. In this carefully conducted investigation with a national twin register they found no concordant monozygotic pairs and two concordant dizygotic pairs. The authors conclude that their data argue against a major genetic influence. There are some limitations in their interpretation. Small numbers and consequently wide confidence intervals mean that their results are not inconsistent with those from previously published studies. Also, the authors relied on recalled diagnosis that might have underestimated the true occurrence of the disease.

There is an undoubted genetic contribution to rheumatoid arthritis which, at least in part, is explained by a susceptibility allele at the HLA-DRB1 locus.[7] Indeed, possession of susceptibility alleles at this locus explains why some monozygotic twins are, and others are not, concordant for rheumatoid arthritis.[8] HLA, however, may explain only about half of the genetic contribution to rheumatoid arthritis,[9] although it has been a difficult task to show genetic susceptibility factors other than HLA consistently among studies.[10 11]

In summary the study by Svendsen et al cannot disprove a genetic component in susceptibility to rheumatoid arthritis. However, their results emphasise that the genetic effects are weak compared with environmental ones in explaining differences in occurrence of the disease. This makes the task more difficult for those attempting large scale linkage studies aimed at revealing the genetic basis for rheumatoid arthritis.

1 Jones MA, Silman AJ, Whiting S, Barrett EM, Symmons DPM. Occurrence of rheumatoid arthritis is not increased in the first degree relatives of a population based inception cohort of inflammatory polyarthritis. *Ann Rheum Dis* 1996;55:89-93.

2 Cooper GS, Miller FW, Pandey JP. The role of genetic factors in autoimmune disease: implications for environmental research. *Environ Health Perspect* 1999;107(suppl 5):693-700.

3 Aho K, Koskenvuo M, Tuominen J, Kaprio J. Occurrence of rheumatoid arthritis in a nationwide series of twins. *J Rheumatol* 1986;13:899-902.

4 Silman AJ, MacGregor AJ, Thomson W, Holligan S, Carthy D, Farhan A, et al. Twin concordance rates for rheumatoid arthritis: results from a nationwide study. *Br J Rheumatol* 1993;32:903-7.

5 MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. *Arthritis Rheum* 2000;43:30-7.

6 Phillips DIW. Twin studies in medical research: can they tell us whether diseases are genetically determined? *Lancet* 1993;341:1008-9.

7 Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibiliby to rheumatoid arthritis. *Arthritis Rheum* 1987;30:1205-13.

8 Jawaheer D, Thomson W, MacGregor AJ, Carthy D, Davidson J, Dyer PA, et al. "Homozygosity" for the HLA-DR shared epitope contributes the highest risk for rheumatoid arthritis concordance in identical twins. *Arthritis Rheum* 1994;37:681-6.

9 Rigby AS, Silman AJ, Voelm L, Gregory JC, Ollier WER, Khan MA, et al. Investigating the HLA component in rheumatoid arthritis: an additive (dominant) mode of inheritance is rejected, a recessive mode is preferred. *Genet Epidemiol* 1991;8:153-75.

10 Cornelis F, Faure S, Martinez M, Prud'homme JF, Fritz P, Dib C, et al. New susceptibility locus for rheumatoid arthritis suggested by a genome-wide linkage study. *Proc Natl Acad Sci U S A* 1998;95:10746-50.

11 Jawaheer D, Seldin MF, Amos CI, Chen WV, Shigeta R, Monteiro J, et al. A genomewide screen in multiplex rheumatoid arthritis families suggests genetic overlap with other autoimmune diseases. *Am J Hum Genet* 2001;68:927-36.

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